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EXAMINER	
BAUSCH, SARAE L	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/516,421	CLERICI ET AL.	
	Examiner	Art Unit	
	Sarae Bausch	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-20* is/are pending in the application.

4a) Of the above claim(s) *5-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3 and 4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 November 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to applicants correspondence mailed 09/11/2007. The amendment to the claims mailed 09/11/2007 has been entered

Election/Restrictions

2. Applicant's election with traverse of group I in the reply filed on 09/11/2007 is acknowledged. The traversal is on the ground(s) that each group represents different embodiments of a single inventive concept for which a single patent should be issued. The response further asserts that even if the groups are drawn to distinct inventions the examiner must still examine the entire application because it would not result in a serious burden. The response further asserts that Shin et al. relates to the use of various polymorphisms for risk of HIV infection and not to determine the existence of Alzheimer's disease and is therefore plainly distinguishable from Shin et al. This is not found persuasive because unity of invention and not restriction practice is applicable to national stage applications (see MPEP 1983.03(d)) As such the arguments submitted with respect to burden has not been considered because this is a national stage application subject to unity of invention and not restriction practice. With regard to applicants arguments that Shin et al. is related to use of polymorphism for risk of HIV and not to determine the existence of Alzheimer's disease it is noted that special technical feature of group I is considered to be analyzing DNA samples from a subject to determine allelic variants. The active process steps do not related back to the preamble and therefore the claims are drawn to detection of allelic variants in IL-10 and not existence of Alzheimer's. Therefore, the special

technical feature of group I is not a contribution of the prior art. Furthermore the technical relationship between the claims can be considered allelic variants of IL-10 and not detection of Alzheimer's as not all the claims require detection of Alzheimer's and therefore there is not a single general inventive concept as allelic variants of IL-10 were known in the art (as per the teachings of Shin et al).

The requirement is still deemed proper and is therefore made FINAL.

3. It is noted that in the response filed on 09/11/2007, applicants elected the variants -1082, -819, and -592 for IL-10, however the claims were amended to recite the elected polymorphisms in the alternative. It was unclear if applicant was electing the specific combination as per the requirements of the restriction mailed 04/11/2007, section 6, page 5. To clarify the response, a telephone interview was conducted with Melissa Hunter-Ensor. During the telephone conversation on 11/16/2007 a election was made to -1082 of IL-10 for claim 1, the specific combination of -1082A for IL-10, -174C for IL-6 and ApoE4 carrier status for claim 3, and the specific combination 1082A for IL-10, -174C for IL-6, ApoE4 carrier status, and -1082A of IL-1 for claim 4. Affirmation of this election must be made by applicant in replying to this Office action.

Drawings

4. The drawings are objected to because the specification does not describe what the lanes in figure 2 represent. Furthermore, the specification on page 9 refers to the alleles of figure 2 however figure 2 demonstrates a gel. It is unclear if the specification on page 9 refers to the alleles in the figure or what is encompassed in the lanes of the gene which is not described.

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Information Disclosure Statement

5. The information disclosure statement filed 11/29/2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has noted that copies of the NPL have been placed in the file and the IDS has been considered. Applicant is reminded that any additional information

disclosure statements that are filed must include a legible copy of each cite foreign patent documentation or non-patent literature publication.

Specification

6. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Rejections - 35 USC § 112- Enablement

7. Claims 1 and 3-4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims

The claims are drawn to a method for the determining the existence of or predisposition to diagnosis of an individual's predisposition to Alzheimer's disease by determining the allelic variant of G to A at -1082 of IL-10 in a subject animal. The claims are limited to additionally analyzing to determine the presence of -174C allele in IL-6 and ApoE4 carrier status. The claims are further limited to additionally analyzing to determine the presence of -1082A allele for IL-1.

The rejected claims encompass analysis of any subject animal, including human and non-human.

The nature of the claims requires knowledge of a correlation between detection of the presence of a -1082A allele of IL-10, -174C allele of IL-6, -1082A allele of IL-1, the status of ApoE4 carrier and diagnosis and predisposition to Alzheimer's disease (AD).

The invention is in a class of inventions which the CAFC has characterized as "the unpredictably arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Guidance in the Specification and Working Examples

The specification teaches the present invention is related to a process of whether IL-10 and IL-6 SNPs were related with the development of AD (pg 3, 2nd last para.). The specification teaches that AD is a clinical syndrome characterized by complex and heterogeneous pathogenic mechanisms (see pg. 1, last para). The specification teaches that the allele e4 of ApoE significantly increases the risk of AD but it is neither necessary nor sufficient for the development of the disease (See pg. 2, 1st paragraph).

The specification asserts that the combination of IL-10 and IL-6 has been found to be more strongly predictive of predisposition to Alzheimer's disease (see pg. 9, 2nd para.). The specification further teaches that ApoE has been associated with sporadic and non-sporadic Alzheimer's and hence a further aspect is the polymorphic allele of IL-10, IL-6, and Apo-E (see pg. 9, 3rd para). The specification further asserts the presence or absence of additional allelic variations of cytokines, specifically IL-10, IL-6, Apo-E and IL-1 (see pg. 9, 5th para.)

The specification demonstrates a working example (example 1) of 47 AD patients and 25 non-demented subjects (see pg. 13, last para). The specification demonstrated whole blood samples were taken and genotyped for IL-10 (see pg. 14). The specification demonstrates genotyping for the promoter region of IL-10 and performing statistical analysis (See pg. 15). The specification teaches that different IL-10 genotypes among AD patients was significantly skewed as shown in table II. However table II demonstration the relation to age of AD onset and table I demonstrates the frequency of different genotypes of AD patients to healthy controls (table I, table II and pg. 16, 1st full para). The specification asserts that the frequency of different genotypes among AD patients was statistically different from health controls and gives a p value of .007, however the specification does not provide any guidance with what the p value represents, its unclear if its the comparison of all alleles of AD to healthy control or specific individual allele of AD to healthy control (see pg. 4, last para). The specification asserts that the presence of the ATA/ATA and GGC/ATA genotypes were associated with earlier age at disease onset with a p value of . 042 demonstrated in table III and the inverse correlation was detected for low IL-10 producing genotypes, table IV. However table III in the specification demonstrates correlation between the different genotypes in AD patients (see pg. 5) and table IV

demonstrates genes Associated with autoimmune/inflammatory disease (see pg. 17-22). Therefore it is unclear which tables example 1 refers to and which tables provide support for the association of IL-10 genotype with AD patients.

The specification demonstrates a working example of 65 AD patients and 65 health controls (See pg. 22, example 2). The specification teaches obtaining blood samples from the individuals and genotyping the samples for IL-10 and IL-6 as well as ApoE genotype (See pg. 23). The specification teaches that the genotype and allele frequencies of the bialleleic polymorphism at position -1082 is reported in table V (see pg. 24). The specification asserts that AD patients who a significantly higher frequency of -1082A which skews the genotype distribution in AD compared to healthy controls (see pg. 24). Table V demonstrates that the A allele is statistically significant in the population of AD patients analyzed however it unclear how the distribution of the allele and p values were determined. According to table V, there were 90 AD patients with the A allele and 36 patients with the G allele, which teaches that 126 AD patients, however the specification teaches that only 65 patients were analyzed. (see pg. 25 and pg. 23). The specification asserts that table VI shows the distribution of IL-6 with AD and healthy control patients. According to table VI, the allele is statistically significant however table VI demonstrates a total of 118 AD patients, 50 with C allele and 68 with G allele but the specification teaches that only 65 patients were analyzed (see pg. 26 and pg. 23). Table VII of the specification demonstrates the IL-10 and IL-6 allele risk for AD however the A allele of IL-10 and the C allele of IL-6 has a p value greater than .05 (see pg. 27).

The specification does not teach any analysis of any non-human animals. The specification does not teach the analysis of IL-1 or ApoE4 carrier in AD patients.

The following is unclear from the teaching in the specification. Although the specification shows a potential relationship between -1082A and human patients, the specification does not teach an association between -1082A and any other non-human animal (pig, rat, horse, cat, etc). Furthermore the data that presents the potential correlation between -1082A IL-10 alone and -174C IL-6 alone does not correspond to the patient population that was tested. It is unclear if there were more patients tested in tables V and table VI or if tables V and VI represented something else. The specification does not teach predictably associating the -1082A of IL-10, -174C of Il-6, ApoE4 carrier or -1082A IL-1, alone or in combination with diagnosis or predisposition to AD in any human or non-human animal.

The unpredictability of the art, the state of the prior art, and the level of skill in the art

While the state of the art and level of skill in the art with regard to detection of a polymorphism in a known gene sequence is high, the level of unpredictability in associating any particular polymorphism with a phenotype is even higher. The level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

The prior art does teaches is replete with evidence that association of -1082A of IL-10, -174C of Il-6, ApoE4 carrier or -1082A IL-1 is unpredictable as larger genotyping studies of different ethnicities of AD patients did not find a predictable correlation between -1082A of IL-10, -174C of Il-6, ApoE4 carrier or -1082A IL-1 alone or in combination with diagnosis or predisposition to AD in any human or non-human animal.

Furthermore, the post filing art is replete with evidence that association of -1082A of IL-10, -174C of Il-6, ApoE4 carrier or -1082A IL-1 is unpredictable. The prior art analyzes several

different populations and larger sample sizes and found that each of the alleles -1082A of IL-10, -174C of Il-6, or -1082A IL-1 is not predictably correlative to diagnosis or predisposition to AD.

The post filing art teaches that -1082A is not associated with AD in different populations. For example, Bagnoli et al. (Neuroscience Letters (207 418:262-265) teaches that there have been conflicting results of IL-10 polymorphisms and their association with AD (See abstract). Bagnoli et al. teach that three studies in Italian and Chinese populations demonstrate that -1082A allele of Il-10 is significantly over represented in AD patients however there are other studies that have not been able to replicate these results and that the role of IL-10 gene in AD may be limited to certain populations (See pg. 262, last para.). Bagnoli et al. analyzed -1082A of 222 AD patients and 179 normal controls (see pg. 263, 1st column, 1st para.). Bagnoli et al. teach many authors have investigated the role of -1082A allele as genetic risk factor for AD with conflicting results. Bagnoli et al. teach a study of 132 AD patients from northern Italy found the -1082A allele was increased in AD patients, in contract a study of 406 German AD patients and 215 Italian AD patients did not replicate these findings, and finally another paper of an American population found no statistical significance in the case-control groups (see pg. 264, 1st column, last para.) Bagnoli et al. teach that no overexpression of the -1082A allele or distribution was found in AD patients, which confirm two Italian studies and a Chinese case-control study (See pg. 264, 1st column, last para.) Therefore, Bagnoli et al. demonstrate the unpredictability of association -1082A allele with AD in a small population study, such as that taught in the instant specification.

Additional post filing art teaches the unpredictability of association -174C allele of IL-6 with AD. Capurso et al. (Exp. Gerontology, 2004, vol. 39, pp. 1567-1573) teach a genotyping

study of AD patients in northern and southern Europe (see abstract). Capuroso et al. teach multiple studies have been conducted to determine the association of -174G/C allele with AD (see table 1). Capurso et al. teach that the association between IL6 -174 G/C promoter polymorphism and increased risk of AD has been evaluated in four ethnic groups with contrasting findings (See pg. 1568, 1st column, 1st para.) Capurso et al. teach analysis of 388 subjects from southern Italy with 168 AD patients (See pg. 1568, 2nd column, last para.). Capurso et al. teach no evidence of an association of IL-6 -174 G/C promoter polymorphism with AD. Capurso et al. teach a study with larger sample size did not show an association with IL-6 -174 G/C promoter polymorphism and risk for AD (see pg. 1571, 2nd column, last para). Capuros et al. teaches the explanation of the conflicting results is unclear but that perhaps there is linkage disequilibrium with another biological relevant locus on chromosome 7 or the polymorphism is due to non-random association with a functional mutation on the gene (see pg. 1572, 1st column, 1st full para) Capurso et al. teaches that a large meta-analysis of genetic association studies with common diseases indicate that only a third to a half of all associations ultimately prove to be significant, emphasizing the importance of larger samples (See pg. 1572, 1st column, 1st full para).

Furthermore, it is unpredictable as to whether or not a sequence comprising -1082A of IL-10, -174C of Il-6, ApoE4 carrier or -1082A IL-1 exists in any non-human organisms, and whether or not detection of a polymorphism in such a sequence in any other organism would be predictive of the risk of immunological disorder and atopy. For example, Mummidi et al. (2000). Mummidi et al. teaches the sequence analysis of the CC chemokine receptor 5 (CCR5) gene in humans and non-primates. Notably, the reference teaches that the substantial

interspecies sequence variation is observed for the cis-regulatory regions of the CCR5 gene (p. 18949, right column, 1st full paragraph). Thus it is entirely unpredictable as to whether or not -1082A of IL-10, -174C of Il-6, ApoE4 carrier or -1082A IL-1, alone or in combination, would be associated with AD in any non-human animal.

Additionally, the prior art teaches that there are many parameters that need to be evaluated prior to using a genetic test to determine a disease and that these parameters yield gaps in information that are needed to complete a thorough screening of a genetic test. Post filing art, Kroese et al. (Genetics in Medicine, vol 6 (2004), p. 475-480) teach genetic tests are heterogeneous in nature and the exact characteristics of a particular genetic test to be evaluated must be tightly defined. Kroese et al. teach that a particular genetic condition may be caused by more than one gene and these variations may be due to deletions and insertions not detected by routine sequence methods. (see page 476, 2nd column, last paragraph). Kroese et al. teach that genetic test is shorthand to describe a test to detect a particular genetic variant for a particular disease in a particular population and for a particular purpose and that it should not be assumed that once the characteristics of a genetic test are evaluated for one of these reasons that the evaluation will hold or be useful for other purposes and all measures of the test performance should be presented with their 95% confidence intervals (see page 477, 1st column, 1st and 2nd full paragraph). Kroese et al. teach that the limitations of our genetic knowledge and technical abilities means that for the moment there are likely to be gaps in the information needed to complete a thorough evaluation of many genetic tests (see page 479, 2nd column, last paragraph). Additional post filing art reveals that most gene association studies are typically wrong.

Furthermore, Ionnidis (Plost Med, 2005, 2(8):e124) teach that most published research findings are false. Ionnidis et al. teach that ill-founded strategy of claiming conclusive research finding solely on the basis of a single study assed by formal statistical significance represented and summarized by p values (see pg. 0696, 2nd column, 1st full para.) Ionnidis et al. teach that research findings are likely to be true that in fields that undertake large studies, such as randomized controlled trials (several thousand subjects randomized) than in small studies such as sample sizes 100 fold or smaller (see pg. 0697, 3rd column, 2nd full para.) Ionnidis et al. teaches that what matters is the totality of evidence and that statistical significance of a single study only gives a partial picture (see pg. 0701, 1st column). Additionally, Hattersley et al. (Lancet, 2005, vol 366, pp. 1315-1323) teaches that the key quality in an association study is sample size (see page 1318, 2nd column, 1st full paragraph). Hattersley et al. teach that sample sizes of thousands are needed to detect variants that are common but have low relative risk and teach that allelic odds ratio of 1.1 to 2.0 requires the number of controls to be in thousands (see page 1318, 2nd column, 1st full paragraph and table 3). Hattersley et al. teach that apparent studies in identifying interesting associations with studies much smaller than implied by table 3 (in the thousands) might suggest that calculations are too pessimistic and small initial studies rarely find the correct result and even when they do they are likely to overestimate the true effect size (see page 1318, 1st column, 1st full paragraph). Hattersley et al. further teaches that emphasis has been on the need for greater stringency in the association studies in order to prove a given association and suggest a p value of $5x10^{-8}$, however arguments from Bayesian perspective suggest that $5x10^{-5}$ should be sufficient to constrain the false discovery rate. It is further relevant to point out that Hegele (2002) teaches the general unpredictability in associating any genotype with a phenotype.

Hegele teaches that often initial reports of an association are followed by reports of non-replication and refutation (p.1058, right col., lns.24-30). Hegele provides a table indicating some desirable attributes for genetic association studies (p.1060), and includes choosing an appropriate significance threshold (see 'Minimized type 1 error (FP)') and replication of results in independent samples (see 'Replication'). Additionally, Hegele teaches the desirability of a likely functional consequence predicted by a known or putative functional domain.

Based on the data presented in the specification and the prior art teachings, it is unpredictable to correlate with the following alleles -1082A of IL-10, -174C of Il-6, ApoE4 carrier or -1082A IL-1, alone or in combination with AD, as the specification does not teach a large sample size, analyze different ethnic groups or provide confidence levels greater than 95% for the following alleles -1082A of IL-10, -174C of Il-6, ApoE4 carrier or -1082A IL-1, alone or in combination. The specification only teaches a subject population of 65 AD patients with statistically significant data for the analysis of an association between -1082A IL-10 and AD patients however the number of patients in the table (Table V) is not consistent with the sample population and further the post filing art demonstrates that in a larger sample size in different ethnicities was demonstrated not to be predictably correlative to AD.

Quantity of Experimentation

Given the lack of guidance in the specification with regard to the association the following alleles -1082A of IL-10, -174C of Il-6, ApoE4 carrier or -1082A IL-1, alone or in combination with AD in "any" animal the quantity of experimentation in this area is extremely large. The skilled artisan would have to perform an extremely large study and include different populations and familial studies for each of the polymorphisms -1082A of IL-10, -174C of Il-6,

ApoE4 carrier or -1082A IL-1, alone or in combination with AD to determine if in fact there was either an association between the polymorphism an individuals and AD in both humans and non-human animals. The results of such a study are unpredictable as evidence by the post filing art (which reflects the current state of the art) and the teachings in the specification. In the instant case, it would be unpredictable as to whether or not the following alleles -1082A of IL-10, -174C of Il-6, ApoE4 carrier or -1082A IL-1, alone or in combination would be responsible for determining the predisposition or diagnosis to AD in any animal. In order to practice the invention as broadly as it is claimed, the skilled artisan would have to perform an extremely large amount of trial and error analysis in a large study to determine if such expression levels would predictable determine a susceptibility to AD. Given the lack of guidance in the specification and the post filing art with respect to accurately testing genetic diseases, such analysis is replete with unpredictable experimentation and is considered undue.

Claim Rejections - 35 USC § 112- Second Paragraph

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1, 3-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and 3-4 is vague and indefinite. The claims are drawn to a method for determining the existence or predisposition to Alzheimer's disease, however the final process

step of claim 1 is detecting by an allelic variant of IL-10. The final process step of claim 3 and 4 is determining the presence of -174C allele of IL-6 and ApoE4 carrier status and determining the presence of -1082A allele for IL-1, respectively. Accordingly the claims are ambiguous because determining the existence or predisposition to Alzheimer's disease and the process step of determining alleles of IL-10, Il-6, ApoE4, or IL-1 does not have to encompass determining the existence or predisposition to Alzheimer's disease and therefore it is not clear that determining -1082 allele of IL-10, 174C allele of IL-6 and ApoE4 carrier status and -1082A allele for IL-1 will *necessarily* result in determining the existence or predisposition to Alzheimer's disease. Therefore, the limitation in the preamble is not recited in the process steps, the metes and bounds of the claim are vague and indefinite, and it is unclear if one necessarily accomplishes what is intended for the method by practicing the recited method step(s). Applicant should amend the claims to indicate how the step of determining the presence of -1082 allele of IL-10, -174C allele of IL-6, ApoE4 carrier status, and -1082A allele for IL-1 results in determining the existence or predisposition to Alzheimer's disease.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Scola et al. (Genes and Immunity, 2002, vol. 3, pp. 30-33).

Scola et al. teach obtaining DNA Samples from of centenarian Italian men and women (see subjects and IL-10 typing, pg. 32). Scola et al. teach -1082A allele was identified (see table 1, pg. 32). Although the claims are directed to determining the existence of or predisposition to Alzheimer's disease, it is noted that the claims are directed to analyzing a DNA sample taken from an individual to determine the allelic variation in IL-10 wherein the polymorphism is a G to A substitution at position -1082. There is no active step relating back to the preamble relating to the determining the allelic variation, accordingly, the claims have been broadly interpreted to encompass detecting the determining the allelic variation of IL-10 wherein the variation is a G to A at position -1082. As such, Scola et al. anticipates the claimed invention.

12. Claim 1 and 3 are rejected under 35 U.S.C. 102(b) as being anticipated by Wang et al. (Mechanism of Aging and Development, 2001, vol. 123, pp. 29-38).

Wang et al. teach obtaining DNA samples from nonagenarians (see subjects and genotyping, pg. 31). Wang et al. teach -1082A allele of IL-10, -174 of IL-6 and A2 + carriage (ApoE4) was identified (see pg. 32, 2nd full para and table 1, pg. 34). Although the claims are directed to determining the existence of or predisposition to Alzheimer's disease, it is noted that the claims are directed to analyzing a DNA sample taken from an individual to determine the allelic variation in IL-10 wherein the polymorphism is a G to A substitution at position -1082 and further comprises analyzing the sample to determine the presence of -174C allele for gene encoding Il-6 and Apoe 4 carrier status. There is no active step relating back to the preamble relating to the determining the allelic variation, accordingly, the claims have been broadly interpreted to encompass detecting the determining the allelic variation of IL-10 wherein the

variation is a G to A at position -1082, the presence of -174C allele for gene encoding Il-6, and ApoE 4 carrier status. As such, Wang al. anticipates the claimed invention.

Claim Rejections - 35 USC § 103

Conclusion

13. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarae Bausch whose telephone number is (571) 272-2912. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free).

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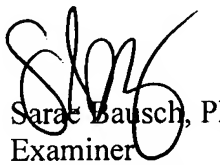

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